Mechanism of Prevention of Postburn Hypermetabolism and Catabolism by Early Enteral Feeding

HIDETAKA MOCHIZUKI, M.D.,* ORRAWIN TROCKI, R.D., M.S., LORENZO DOMINIONI, M.D.,†
KIM A. BRACKETT, PH.D., STEPHEN N. JOFFE, M.D., J. WESLEY ALEXANDER, M.D., SC.D.

This study was performed to investigate the mechanism whereby immediate enteral feeding after burn injury reduces postburn hypermetabolism and hypercatabolism. Fifty-seven burned guinea pigs (30% TBSA) were divided into three groups: A (N = 19), given 175 kcal/kg/day beginning 2 hours after burn; B (N = 20), given 175 kcal/kg/day with an initial 72-hour adaptation period; and C (N = 18), given 200 kcal/kg/day with the same adaptation period as B. Resting metabolic expenditure (RME) on PBD 13 was lowest in group A (109% of preburn level), compared with group B (144%, $p < 0.001$) and group C (137%, $p < 0.01$). On PBD 1, group A had the greatest jejunal mucosal weight and thickness ($p < 0.001$), and mucosal weight had negative correlations with plasma cortisol ($r = 0.829$, $p < 0.001$) and glucagon ($r = 0.888$, $p < 0.001$). Two weeks after burn, urinary vanillyl mandelic acid (VMA) excretion, plasma cortisol, and glucagon were lowest in group A ($p < 0.05$ to $p < 0.01$). These hormones also significantly correlated with RME ($p < 0.01$ to $p < 0.001$). These findings suggest that immediate postburn enteral feeding can prevent hypermetabolism *via* preservation of gut mucosal integrity and prevention of excessive secretion of catabolic hormones.

From the Shriners Burn Institute, and the Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio

IN THE FIRST FEW DAYS after severe burn injury, nutritional management is regularly neglected because of the need for aggressive fluid resuscitation and postburn paralytic ileus often seen at this stage.[1] As a consequence, patients usually lose lean body mass and become nutritionally depleted, even during the resuscitation period. Subsequently, severe burn injury is characterized by a marked hypermetabolic response, hypercatabolism, and even more severe loss of lean body mass.[2-4] Aggressive nutritional support to meet the increased energy expenditure has been considered essential for the management of burn patients.[5-7] However, it is often difficult to meet the increased energy needs by oral or enteral feeding because of gastrointestinal (G.I.) intolerance to the higher amount of nutrients. Intravenous (I.V.) hyperalimentation is usually contraindicated because of the location of the burn injury and the increased risk of sepsis by this feeding method. If the postburn hypermetabolic response could be reduced, it would be highly advantageous for the nutritional management of burn patients.

In a previous study, we found that immediate postburn intragastric feeding in burned guinea pigs not only reduced the postburn hypercatabolism and maintained a better postburn nutritional state, it also reduced the hypermetabolic response.[8] Since increased evaporative heat loss from the wound surface[9] and increased catabolic hormonal secretion[2,10] are considered to be the main causes of hypermetabolic response, as suggested by investigations conducted during the past 30 years,[2,11-14] we studied the effects of early feeding on secretion of the catabolic hormones and their relationship to gut mucosal integrity.

Materials and Methods

Preparation of the Animals

Sixty-four female Hartley guinea pigs (409 ± 3 g) underwent catheter gastrostomy by placing one end of a Silastic tube (size: 0.062 inches inside diameter (I.D.), 0.095 inches outside diameter (O.D.), Dow Corning Co., Midland, MI) into the stomach under general anesthesia [ketamine HCl, 50 mg/kg, acepromazine maleate, 0.2 mg/kg, atropine sulfate, 0.04 mg/kg, intramuscularly (I.M.)]. Prior to the operation for gastrostomy, all animals were adapted for at least 10 days to constant laboratory

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* Present address: Department of Surgery, National Defense Medical College, Tokorozawa, Saitama, 359, Japan.

† Present address: Department of Surgery, University of Pavia, Pavia 27100, Italy.

In conducting the research described in this article, the investigators adhered to the "Guide of Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Science, National Research Council.

Reprint requests: Dr. J. Wesley Alexander, Shriners Burns Institute, 202 Goodman Street, Cincinnati, OH 45219.

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TABLE 1. *Grouping of the Animals and Dietary Schedules*

	Daily Caloric Intake After Burn (kcal/kg/day)				Cumulative Caloric Intake/14 days (kcal/kg)
	Day 0	PBD 1*	PBD 2	PBD 3 to 14	
I (EF)	175 (N = 19)	175 (12)	175 (12)	175 (12)	2450
II (175–72 hr)	1† (N = 20)	58 (15)	117 (15)	175 (15)	2101
III (200–72 hr)	1† (N = 18)	67 (13)	133 (13)	200 (13)	2401
		← Adaptation period → for Groups II and III			

* On postburn day 1, seven animals of Group I and five in each of Groups II and III were sacrificed.

† Received lactated Ringer's solution 80 ml/24 hours.

conditions at a temperature of 26 C, being fed Wayne Guinea Pig Pelleted Diet (Wayne Feeds Research Division, Libertyville, IL) and water *ad libitum*. After the operation, they were caged individually under the same laboratory conditions and fed as before surgery for an additional 7 days. During that time, the animals recovered completely from the surgery and regained the ten per cent of body weight that they had lost immediately after the operation. Fifty-seven animals underwent an identical 30% total body surface area (TBSA) full thickness flame burn on the back under general anesthesia and were resuscitated with an intraperitoneal injection of 20 ml lactated Ringer's (LR) solution. Immediately after burn, they were placed into individual metabolic cages at the same laboratory conditions. The gastrostomy tube was connected to a pump-controlled continuous enteral infusion system (Holter TM Pump Model 903, Criticon, Inc., Tampa, FL) with a swivel between the gastrostomy tube and infusion system so that the animal could move freely in the cage during the experimental period.[15] The other seven animals did not undergo burn injury and were used for preburn controls (preburn group).

Diets and Enteral Feeding

The animals bearing the 30% TBSA burn were divided into three groups according to three different dietary schedules. The animals in Group I (N = 19) received 175 kcal/kg/day beginning 2 hours after burn (EF group, Table 1). This amount of daily calories was given to meet the measured energy expenditure of freely fed guinea pigs during the first 2 weeks after a 30% TBSA full thickness burn (178 ± 5 kcal/kg/day).[8] Group II (N = 20) received the same daily calories as the EF group (175 kcal/kg/day) after an initial 72-hour adaptation period (175 kcal-72 hr group). Group III (N = 18) received 200 kcal/kg/day with the same adaptation period as the second group (200 kcal-72 hr group). Only the EF group received full concentrated diet from the beginning of tube feeding. The initial 72-hour adaptation period for other two groups was designed to simulate the nutritional adaptation period often used for the management of burned patients. During the first 24 hours of the adaptation period, those two groups received only 80 ml of lactated Ringer's solution intragastrically. For the second 24 hours, they received one-third of their planned caloric intake and then two-thirds for the next 24 hours. Subsequent to the 72-hour adaptation period, they received full caloric intake. The cumulative caloric intake in the EF group during the entire experimental period (14 days) was almost the same as that of 200 kcal-72 hr group (2450 *vs.* 2401 kcal/kg, respectively), but it was greater than that of 175 kcal-72 hr group (2101 kcal/kg). The composition of the diet was identical for each group (Table 2). Twenty per cent of total calories were given as milk whey protein (Promix, Navaco Labs, Phoenix, AZ), 68% as glucose polymer (Polycose, Ross Labs, Columbus, OH), and 12% as lipid from safflower oil (Microlipid, Organon, Inc., West Orange, NJ). The N:nonprotein calorie ratio was 1:100. All diets were supplemented with the same amount (16 ml) of a balanced electrolyte and vitamin solution daily. Arginine HCl was also supplemented because of its known effect on wound healing.[16] This formula was found to provide good nutritional support for burned guinea pigs in previous studies.[17,18] The volume of the diet providing the planned daily caloric load, even for the adaptation period, was diluted with water to a final volume of 100 ml (2500 ml/m^2), and the diet was infused continuously over 24 hours. Any oral intake of food or water was forbidden during the postburn period. The burn wounds developed a dry eschar and no treatment for the wounds was performed.

Schedule of Sacrifice

Seven unburned guinea pigs bearing a catheter gastrostomy (preburn group) were sacrificed by total exsanguination *via* cardiac puncture under general anesthesia

(sodium pentobarbital, 500 mg/kg, I.M.) on the seventh postoperative day to provide control for intestinal and hormonal investigations in the postburn groups. Seven animals of the EF group and five animals each of 175 kcal-72 hr and 200 kcal-72 hr groups were sacrificed similarly on postburn day (PBD) 1 for intestinal and hormonal studies. Since both of the groups with a 72-hour adaptation period had received only lactated Ringer's solution to the point of sacrifice, the ten animals from these two groups had the same nutritional and hormonal state and were grouped together (LR group). Twelve animals of the EF group, 15 animals of the 175 kcal-72 hr group, and 13 animals of the 200 kcal-72 hr group were sacrificed by the same method on PBD 14. All animals received tube feeding according to each dietary schedule until just before sacrifice.

Evaluation of Nutritional State

Each animal was weighed daily. Nitrogen (N) balance was calculated daily by subtracting urinary and fecal N from dietary N using a previously described method.[8] Then the cumulative N balance for the 14-day intragastric tube feeding was calculated. Since the burn wound consisted of dry eschar that did not significantly exudate for the experimental period, N loss was thought to be negligible and it was not included in the N balance calculations. The following parameters were determined after the sacrifice on PBD 14. Serum albumin concentration was determined by the bromocresol green method. Serum transferrin was measured by nephelometry (Immunochemistry Analyzer II, Beckman Instruments, Inc., Fullerton, CA), using anti-human transferrin serum (Transferrin Reagent Kit, Beckman Instruments, Inc., Brea, CA). It was shown preliminarily that this anti-human transferrin serum cross reacted with guinea pig transferrin.[17] The third component of complement (C3) was also measured by nephelometry, using anti-guinea pig C3 serum (Coppel Labs, West Chester, PA). The liver was weighed and N concentration was measured on a homogenized sample as described before,[18] then the total N content for the liver was calculated. The gastrocnemius muscles were dissected free bilaterally and their wet weights were measured. All animals were completely skinned, evicerated, decapitated, and the feet excised. The wet weight of the remaining carcass, which consisted of skeleton and muscular-fascial structures, was measured. Diarrhea was defined as the discharge of nonformed stool for at least 2 days, but it was not treated.

Measurement of RME

Resting metabolic expenditure (RME) was measured on the seventh postoperative day as preburn level, and on PBDs 2, 6, 9, and 13 by the indirect calorimetry method, measured the O_2 consumption and CO_2 production with a computerized Respiratory Gas Monitor (Webb Associates, Inc., Yellow Springs, OH).

TABLE 2. *Composition and Components of the Diet*

Caloric composition*			
Total kcal/l	1000		
kcal from protein	200		
kcal from carbohydrate	680		
kcal from lipid	120		
Nutrient source			
Protein (Promix®) (g/l)†			62.5
Carbohydrate (Polycose®) (ml/l)‡			340
Lipid (Microlipid® (ml/l)§			27
Arginine HCl (g/l)			2.5
Vitamin and electrolyte (ml/day/animal) (see below)			16
Vitamin and electrolyte solution			
NaCl (2.5 mEq/ml)	24 ml	Cu	0.5 mg
KCl (2 mEq/ml)	10 ml	MVI concentrate®‖	5 ml
K-acetate (2 mEq/ml)	24 ml	Vitamin C	500 mg
K-phosphate (3 mM/ml)	10 ml	Vitamin E	100 mg
Ca-gluconate (0.1 g/ml)	50 ml	Choline chloride	500 mg
$MgSO_4$ (4 mEq/ml)	24 ml	Folic acid	2 mg
Zn	6 mg		
		Total	160 ml

* N:nonprotein calories = 1:100.
† Navaco Laboratories, Phoenix, Arizona.
‡ Ross Laboratories, Columbus, Ohio.
§ Organon, Inc., West Orange, New Jersey.
‖ USV Laboratories, Tuckahoe, New York.

Intestinal Mucosal Investigation

The whole small intestine was quickly removed at sacrifice. A 10-cm segment of proximal jejunum, beginning 15 cm beyond the pyloroduodenal junction, was excised for mucosal sampling after using a uniform degree of tension by suspending a standard weight from one end of the gut. The mucosa of jejunal segment was scraped with a stainless steel spatula according to the method of Levine et al.[19] and the wet weight of mucosa was measured. The N content in the scraped jejunal mucosa was determined on the homogenized sample by the same method used for liver N determination. A 10-cm segment of ileum was taken from the middle part of the small intestine, and the ileal mucosa was scraped and weighed in the same manner as for the jejunum. A 1-cm jejunal segment was taken just distal to each 10-cm jejunal segment mentioned above and fixed in 10% formaline for histological preparation. After fixation, these samples were sliced perpendicularly to the stretched mucosal plane so that the mucosal thickness could be measured precisely. The widest five points of mucosal thickness (from top of villus to the basal level of lamina muscularis mucosae) were measured in each sample using a computerized image analyzer (Videoplan-Version #5, Carl Zeiss, Inc., Thornwood, NY) connected to a light field microscope, then the mean value was calculated. An additional small

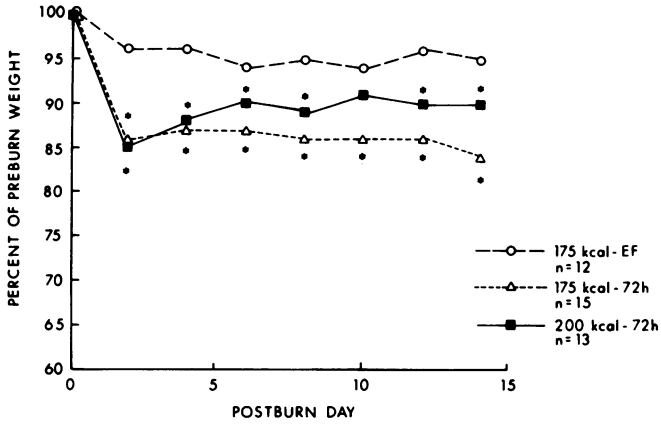


FIG. 1. Changes of body weight (expressed as % of preburn weight) in burned guinea pigs with three different dietary schedules. * Significantly different from EF group ($p < 0.05$ to $p < 0.0001$).

section of jejunum was sampled from preburn, EF-1PBD and LR groups, then fixed in 2.5% buffered glutaraldehyde for scanning electron microscopy (SEM). The specimens were coated with a gold/palladium alloy, and jejunal mucosal thickness was measured by SEM in those three groups. Before the processing for SEM, samples were fractured to expose a cross-sectional view. Then the tilt angle of the specimen was adjusted so that the angle of the area being measured was perpendicular to the electron beam for the determination of accurate mucosal thickness.

TABLE 3. *Nutritional Measurements at PBD 14*

Parameters	Groups		
	EF	175 kcal–72 hr	200 kcal–72 hr
Body weight (% of preburn wt)	95.2 ± 1.3 (N = 12)	84.4 ± 1.7* (N = 15)	90.7 ± 1.9‡ (N = 13)
Carcass weight (% of preburn wt)	32.2 ± 0.5 (N = 12)	26 ± 0.8† (N = 7)	28.5 ± 0.6* (N = 7)
Average weight of gastrocnemius muscle (g)	1.12 ± 0.03 (N = 12)	0.86 ± 0.03† (N = 7)	0.98 ± 0.04§ (N = 7)
Total nitrogen content in liver (mg)	528 ± 29 (N = 10)	453 ± 22‡ (N = 14)	485 ± 21 (N = 13)
Cumulative nitrogen balance (mg/animal)	1184 ± 194 (N = 7)	1279 ± 234 (N = 7)	1221 ± 283 (N = 7)
Serum albumin (g/dl)	3 ± 0.1 (N = 11)	2.5 ± 0.2‡ (N = 11)	2.9 ± 0.3 (N = 9)
Serum transferrin (% of normal)	150 ± 9 (N = 9)	129 ± 3‡ (N = 14)	144 ± 14 (N = 9)
C3 (% of normal)	150 ± 8 (N = 9)	103 ± 9§ (N = 14)	152 ± 10 (N = 9)

( ) Number of animals; mean ± SEM.
* $p < 0.001$
† $p < 0.0001$
‡ $p < 0.05$
§ $p < 0.01$
Compared with EF group.

The mucosal surface appearance of each sample was also observed by SEM.

Measurement of Hormones

Urinary vanillyl mandelic acid (VMA) excretion was measured during the preburn period, on PBD 1–2 (24–48 hours after burn) and PBD 12–13. A 24-hour urine specimen of each stage was collected in a glass bottle containing 5 ml of 3N hydrochloric acid to provide a final pH below 3, which makes urinary catecholamines stable at room temperature.[20] VMA concentration in urine was determined by high pressure liquid chromatography,[21,22] using a fixed wavelength ultraviolet detector 280 nm (Waters Associates, Inc., Milford, MA). Daily urinary VMA excretion at each period was calculated. Plasma cortisol and glucagon were measured preburn and on PBDs 1 and 14. Plasma cortisol, which is the predominant glucocorticoid in guinea pigs,[23] was determined by radioimmunoassay,[24] using rabbit anti-cortisol-3-carboxymethyl oxime serum (supplied from L. S. Srivastava, Ph.D., Endocrinology and Metabolic Division, University of Cincinnati College of Medicine, Cincinnati, OH). Plasma glucagon was measured by radioimmunoassay using antibody specific for C-terminal-to central region of glucagon (Queen's University of Belfast, Northern Ireland, code YY89).[25] The C-terminal-to central immunoreactivity is considered pancreatic glucagon. Blood glucose was determined by the hexokinase method.

The measurements mentioned above were not always done on all animals because of insufficient sample size or accident. In all such cases, however, sufficient samples were available for statistical analysis selected randomly from each group.

The results of this study were expressed as means ± SEM and analyzed statistically by unpaired Student's t-test or by linear regression analysis.

Results

All animals survived to the end of the experimental period. The EF group did not suffer from diarrhea or other side effects of very early intragastric feeding, such as vomiting or abdominal distension.

Nutritional State

The course of body weight change is shown in Figure 1. Animals in the EF group maintained their weight at about 95% of preburn weight throughout the experimental period. In contrast, the two groups with a 72-hour adaptation period showed severe weight loss, approximately 15% of preburn weight, within 72 hours after burn, and they did not regain their weight loss during the 2-week period. Thus, animals in the EF group were significantly

TABLE 4. *Resting Metabolic Expenditure*

	RME (kcal/kg/day)					% RME (% of Preburn)			
	Preburn	PBD 2	PBD 6	PBD 9	PBD 13	PBD 2	PBD 6	PBD 9	PBD 13
EF N = 10	158 ± 5	172 ± 8	179 ± 5	177 ± 6	174 ± 6	109 ± 4	113 ± 3	112 ± 4	109 ± 4
175 kcal-72 hr N = 9	144 ± 5	167 ± 8	199 ± 14	212 ± 13*	206 ± 11†	116 ± 6	138 ± 9*	148 ± 10‡	144 ± 7§
200 kcal-72 hr N = 7	159 ± 8	175 ± 7	180 ± 11	199 ± 14	214 ± 10‡	110 ± 5	113 ± 8	125 ± 8	137 ± 10‡

Mean ± SEM.

* $p < 0.05$
† $p < 0.02$
‡ $p < 0.01$
§ $p < 0.001$
} Compared with EF group.

heavier than the other two groups from PBD 2 to the end of the experimental period. Other nutritional measurements at PBD 14 are shown in Table 3. The 175 kcal-72 hr group, which received the same daily caloric intake as the EF group after the adaptation period, showed a significantly depleted nutritional condition compared with the EF group, except for cumulative N balance. The 200 kcal-72 hr group, which received the same amount of cumulative caloric intake as the EF group for 14 days, was also significantly more depleted than the EF group, not only in body weight but also in carcass weight and gastrocnemius muscle weight. Although there was no statistical difference, total N content in the liver and serum transferrin levels were lower in the 200 kcal-72 hr group compared to the EF group. Albumin and C3 levels were similar to the 200 kcal-72 hr group and the EF group.

RME

The preburn RME was at the same level in all groups (Table 4). Although all groups showed the same RME on PBD 2, the two groups with a 72-hour adaptation period gradually increased their RME thereafter, but RME did not rise in the EF group. When RME is expressed as per cent of preburn level (5 RME), the trend can be recognized more clearly (Table 4, Fig. 2). On PBD 13, RME of two groups with a 72-hour adaptation period reached approximately 140% of preburn level, significantly higher than the EF group.

Intestinal Mucosa

On PBD 14, there was no statistically significant difference in intestinal mucosal weight, mucosal N content, and mucosal thickness among the three groups (Table 5). However, in the early stage after burn (PBD 1), jejunal mucosal weight, mucosal N content, and mucosal thickness showed an identical trend between groups. Ileal mucosal weight was also determined and it showed the same tendency found for the jejunal mucosa. Compared with the preburn controls, the EF group had no decline in mucosal measurements on PBD 1, whereas the LR group showed a significant decline from the preburn group in all mucosal measurements. Although the mucosal thickness measured with light field microscope was greater than that measured with SEM, the trend of the results from these two methods was the same among the three groups. The difference in measured thickness between two methods was thought to be due to the different method for fixation of specimens. Jejunal mucosal appearance at preburn and PBD 1 samples by SEM are shown in Figures 3A, 3B, and 3C. The jejunal villi of the preburn group were predominantly tongue-shaped with narrow spaces between individual villi (Fig. 3A). In the LR group, villi were a mixture of tongue-shaped and narrow, finger-shaped villi, with reduction of villous width and wider spaces (Fig. 3B). Villi of the EF group were predominantly tongue-shaped with some broadening of the villi compared to those of preburn group. The intervillous spaces were

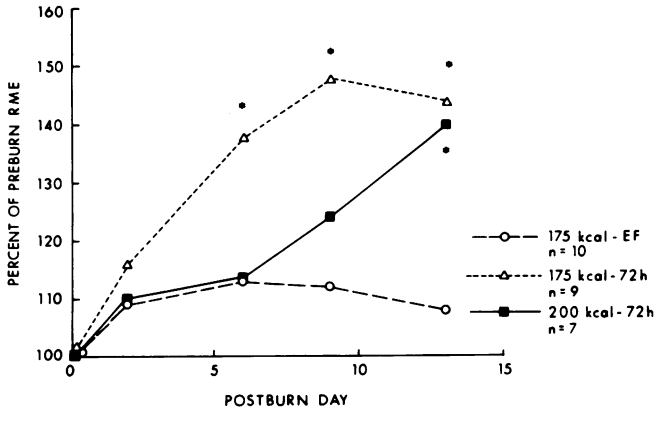


FIG. 2. Changes of resting metabolic expenditure (expressed as % of preburn level, *i.e.*, % RME) in burned guinea pigs with three different dietary schedules. * Significantly different from EF group. The 175 kcal-72 hr group showed a statistically significant difference from PBD 6 to PBD 13 ($p < 0.05$ to $p < 0.001$). The 200 kcal-72 hr group showed a significant difference only on PBD 13 ($p < 0.01$).

TABLE 5. *Intestinal Mucosal Weight, Nitrogen Content and Thickness*

			Preburn	PBD 1		PBD 14		
			Fed *Ad Lib*	EF	LR*	EF	175 kcal 72 hr	20 kcal 72 hr
Mucosal weight (mg/10 cm)		Jejunum	430 ± 26 (7)	375 ± 18 (7)	221 ± 23¶·‡‡ (10)	525 ± 44 (12)	527 ± 33 (7)	556 ± 58 (7)
		Ileum	318 ± 45 (7)	314 ± 19 (7)	208 ± 19§·†† (10)	359 ± 17 (12)	351 ± 15 (7)	373 ± 19 (7)
Mucosal nitrogen (mg/10 cm)		Jejunum	12.8 ± 1.4 (7)	11.4 ± 0.5 (7)	9.0 ± 0.9§·** (7)	11.6 ± 1.2 (7)	11.8 ± 0.9 (7)	13.2 ± 0.7 (7)
Mucosal thickness (μm)	LFM†	Jejunum	990 ± 25 (6)	1017 ± 19 (7)	697 ± 21¶·‡‡ (7)	1003 ± 20 (7)	973 ± 44 (7)	977 ± 16 (6)
	SEM‡	Jejunum	770 ± 19 (5)	798 ± 25 (5)	689 ± 13‖·†† (5)		N.D.	

( ) Number of animals; mean ± SEM; N.D.: not determined.
* Received only lactated Ringer's solution for 24 hours.
† Measured with light field microscope.
‡ Measured with scanning electron microscope.

§ $p < 0.05$
‖ $p < 0.01$
¶ $p < 0.001$
} Compared with preburn group.

** $p < 0.05$
†† $p < 0.01$
‡‡ $p < 0.001$
} Compared with EF group on PBD 1.

apparently narrower than those of the LR group (Fig. 3C).

Hormones

On PBD 1, the fed state blood glucose levels of the EF group were not higher than the fasted state levels of the LR group in spite of early enteral feeding (Table 6). Plasma cortisol, glucagon levels on PBD 1 were significantly elevated in the LR group but were almost the same in the EF group as in preburn controls. The LR group showed significantly higher levels compared not only with the preburn group but also the EF group. Although the 24-hour urinary excretion of VMA was at a trace level for preburn animals, burned groups all showed significant amounts of excretion 24 to 48 hours after burn (PBD 1–2). Differing from the trend to plasma cortisol and glucagon, urinary VMA excretion on PBD 1 showed no significant difference among the three groups.

On PBD 14, plasma cortisol and glucagon levels of the EF group were almost the same as on PBD 1, and significantly lower than those of both groups with a 72-hour adaptation period. The 24-hour urinary VMA excretion from PBD 12 to PBD 13 showed exactly the same trend as the plasma cortisol and glucagon levels. It was lowest in the EF group and significantly higher in two groups with a 72-hour adaptation period, both excreting almost the same amount of VMA. The EF group maintained the same level of VMA excretion as on PBD 1–2. The comparison of urinary VMA excretion between PBD 1–2 and PBD 12–13 for each animal is shown in Figure 4. The animals in the EF group declined slightly, and, although there was an increased trend as a whole, the individual animals with a 72-hour adaptation period did not show a constant pattern. Some maintained their excretion at a stable level, some increased markedly, and some greatly decreased VMA excretion.

Correlations

There were very close negative correlations between plasma hormone levels and jejunal mucosal weight on PBD 1. Plasma cortisol level had a significant negative correlation with jejunal mucosal weight ($r = 0.829$, $p < 0.001$, Fig. 5) as did plasma glucagon ($r = 0.888$, $p < 0.001$, Fig. 6). In the early postburn period (PBD 1–2), there was a significant correlation between % RME and urinary VMA excretion ($r = 0.548$, $p < 0.05$, Fig. 7), which became even more significant in the late stage of the experimental period, also (PBD 12–13, $r = 0.739$, $p < 0.005$, Fig. 8). Two weeks after burn, % RME also significantly correlated with plasma cortisol level ($r = 0.862$, $p < 0.001$, Fig. 9) and plasma glucagon level ($r = 0.731$, $p < 0.01$, Fig. 10). At no time was there a correlation between blood glucose and hormones, or glucose and jejunal mucosal weight.

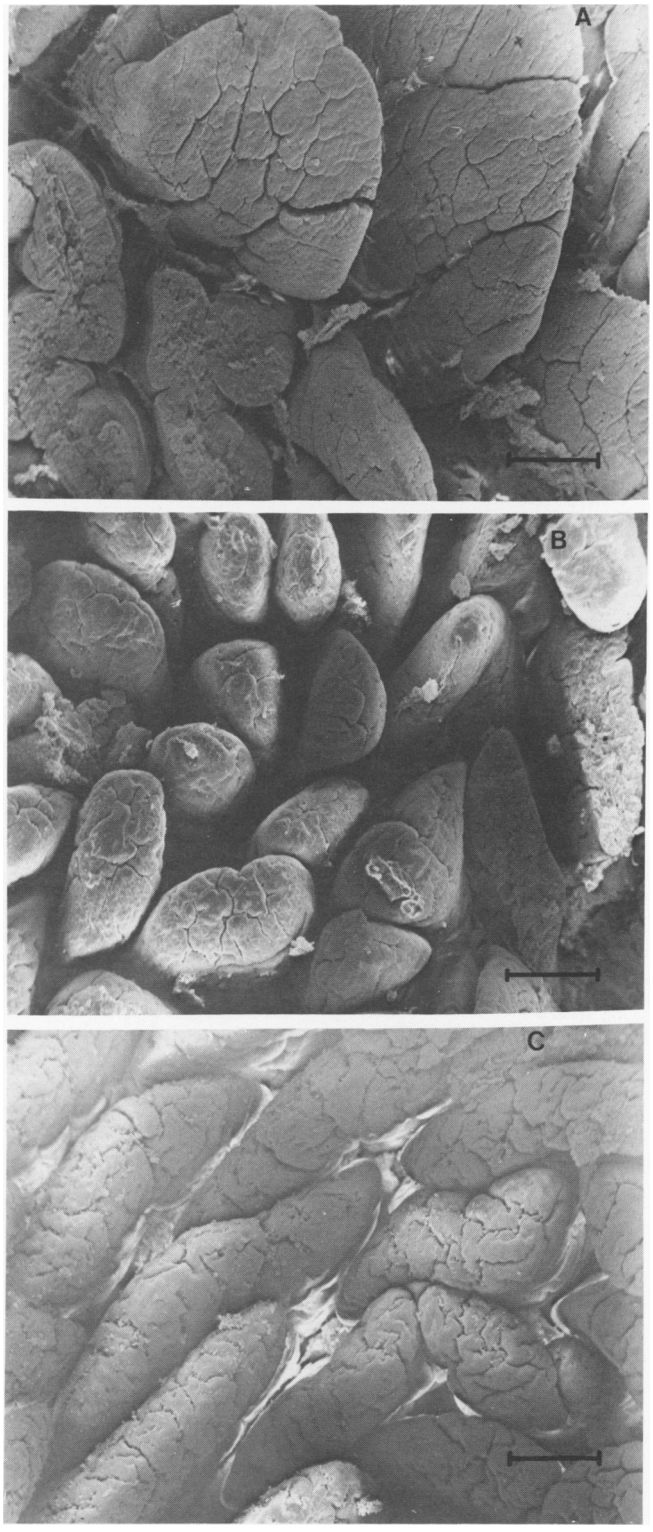
Discussion

Severely burned patients generally show a marked hypermetabolic response and their energy expenditure increases to almost twice normal as burn size exceeds 50% of TBSA.[2,6,26] This hypermetabolic response is accompanied by severe catabolism, which is characterized not only by the loss of lean body mass[3,4,6,27–29] but also by a progressive decline of host defenses[7,30] that impairs survival. Nutritional support has been considered an essential part of postburn management to minimize the catabolic

loss, and vigorous nutritional therapy has been reported to have very beneficial results.[5,6,30] However, enteral feedings are usually not begun during the resuscitation period since the digestive tract is considered to be functioning poorly. While it is generally accepted that nutritional support must be initiated by the fourth postburn day and should achieve either positive or neutral energy balance by the seventh postburn day,[1,31] using this protocol, it is difficult to avoid a severe loss of lean body mass that has been accepted as an inevitable response to a major burn injury.[32]

Reduction of postburn hypermetabolism would appear to be beneficial because of the difficulty in satisfying the markedly increased nutritional needs of the severely burned patient. Increased evaporative heat loss from the wound surface has been considered one cause of the hypermetabolism.[9,12,14] but increased secretion of the catabolic hormones (catacholamines, glucagon, and cortisol) has been thought to be the major mediator.[2,10,13,33] According to the former hypothesis, an increase of ambient temperature should decrease the loss of body heat and decrease metabolic rate. However, this is only partly effective in controlling hypermetabolism.[34] Administration of α- or β-blockade[2,23] to block the increased activity of catecholamines is partly effective but cannot be used for long-term therapy in burned patients,[35] and cortisol and glucagon blockade cannot be accomplished clinically. The present consensus for management of hypermetabolism in burned patients is, therefore, to minimize metabolic demand by maintaining the patient in a warm environment and covering the wound, and to maximize feeding[28,35] to meet excessive demands.

Our results show that immediate postburn intragastric feeding with sufficient calories to meet energy expenditure of postburn period had the effect of reducing the hypermetabolic response (Table 4, Fig. 2) and also provided optimal preservation of the nutritional state (Fig. 1, Table 3). Wolfe *et al.*[36] reported that the food intake in early postburn period causes a hypermetabolic response to burn injury in another burned guinea pig model (20–25% TBSA burn). However, in their study, the administered calories (approximately 135 kcal/kg/day) were delayed (beginning PBD 1) and did not meet energy expenditure of burned guinea pigs. With an insufficient amount of calories, we have also noticed an abrupt increase of RME in our burned guinea pig model, even though the feeding was initiated immediately after burn (PBD O: received 87 kcal/kg/day, PBD 1: received 155 kcal/kg/day).[8] Similarly, with a 72-hour adaptation period, during which the caloric intake was extremely insufficient, we have also demonstrated the same hypermetabolic response as seen in the previous study.[8] It is therefore likely that insufficient food supply in the early postburn period causes an increase of RME following burn. Wilmore et al.[37] reported that post-



FIGS. 3A–C. Mucosal villous appearance of jejunum taken by scanning electron microscope at the same power (×1500). The specimens were coated with gold/palladium alloy. The scales at the right bottom indicate 10 μ. *A, top.* Jejunal mucosa of preburn group. Villi were predominately tongue-shaped with small spaces between individual villi, *B, middle.* Jejunal mucosa of LR group (PBD 1). Villi were a mixture of tongue and narrow, finger-shaped. *C, bottom.* Jejunal mucosa of EF group (PBD 1). Villi were predominately tongue-shaped with some broad ridges.

TABLE 6. *Blood Glucose and Hormones*

	Preburn	PBD 1		PBD 14		
	Fed *Ad Lib*	EF	LR*	EF	175 kcal 72 hr	200 kcal 72 hr
Blood glucose (mg/dl)	123 ± 10 (7)	138 ± 9 (7)	142 ± 7 (7)	152 ± 7 (8)	188 ± 12§ (6)	164 ± 18 (9)
Plasma cortisol (μg/dl)	48.1 ± 6.1 (7)	61.1 ± 2.5 (7)	122.8 ± 12.8‡¶ (7)	59 ± 8.5 (8)	116.6 ± 17.9‖ (7)	123.6 ± 24.1§ (10)
Plasma glucagon (pg/ml)	19.1 ± 2.8 (7)	26 ± 6.8 (7)	313.7 ± 60†‖ (7)	23 ± 5 (7)	101.8 ± 17.6‖ (6)	76 ± 10.1¶ (7)

		PBD 1-2			PBD 12-13		
		EF	175 kcal 72 hr	200 kcal 72 hr	EF	175 kcal 72 hr	200 kcal 72 hr
Urinary VMA Excretion (μg/day)	Trace (6)	13.2 ± 1.3 (7)	20.3 ± 4.2 (7)	12.9 ± 1.5 (6)	11.1 ± 0.7 (7)	22.3 ± 3.9§ (7)	25.6 ± 5.5§ (6)

( ) Number of animals; mean ± SEM.
* Received only lactated Ringer's solution for 24 hours.
† $p < 0.01$, ‡ $p < 0.001$ } Comparison between preburn and PBD 1.
§ $p < 0.05$, ‖ $p < 0.01$, ¶ $p < 0.001$ } Compared with EF group.

burn RME could not be changed with different levels of caloric intake. Their study did not indicate when feedings were begun and the study was not performed from the early postburn period. Thus, their results cannot be considered contradictive to our findings.

The present study has attempted to investigate the mechanism by which immediate postburn intragastric feeding could maintain the metabolic response at a very low level and reduce hypercatabolism after burn. VMA is the main metabolite of catecholamines, and the quantitative determination of urinary excretion is considered to provide a more reliable measure of catecholamine secretion than epinephrine and norepinephrine when catecholamine secretion is very much increased.[20] On PBD 1-2, RME and urinary VMA excretion were related (Tables 4, 6); namely, they were higher in burned groups than preburn, but there was no statistical difference among burned groups. Since there was a significant correlation between % RME and urinary VMA excretion during this period (Fig. 7), catecholamine excretion seemed to be clearly related to the slight hypermetabolic response found soon after injury. Plasma cortisol and glucagon levels were strikingly higher in the LR group than the EF group on PBD 1 (Table 6), but their association with hypermetabolism on PBD 2 could not be examined in this study since the animals were sacrificed on PBD 1. It has been shown that plasma cortisol stimulates protein catabolism and amino acid mobilization from the periphery in the postburn period.[10,38]

While a variety of studies have suggested a relatively minor role for glucagon in the catabolic response to burn injury,[9,38,39] other studies show that this hormone increases

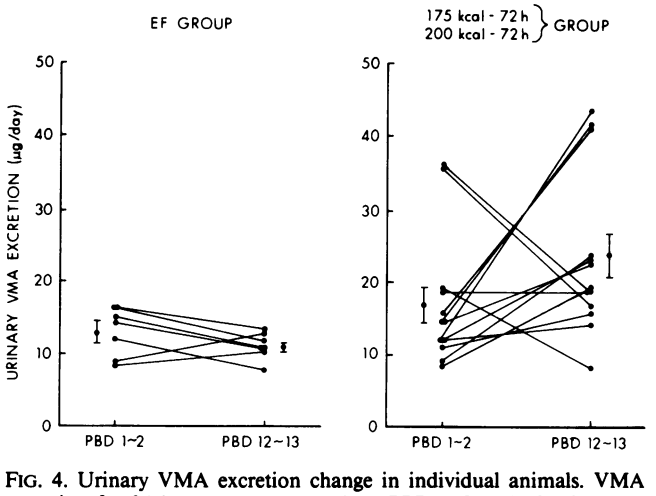


FIG. 4. Urinary VMA excretion change in individual animals. VMA excretion for 24 hours was measured on PBD 1-2 and 12-13. Mean ± SEM of each stage is shown also.

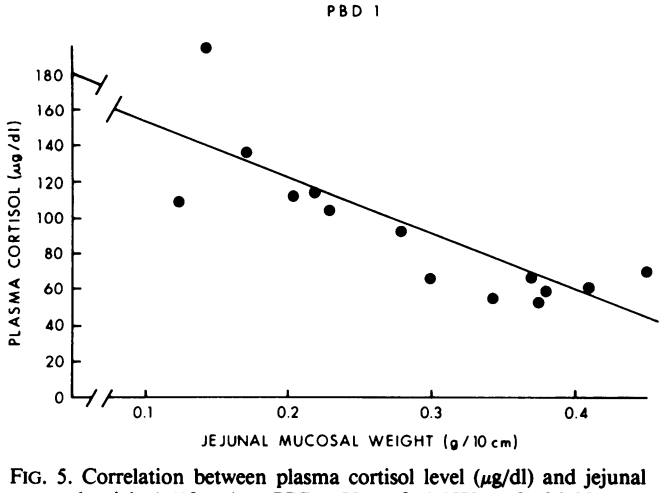


FIG. 5. Correlation between plasma cortisol level (μg/dl) and jejunal mucosal weight (g/10 cm) on PBD 1. $Y = -314.45X + 181.86$, $N = 14$, $r = 0.829$, $p < 0.001$.

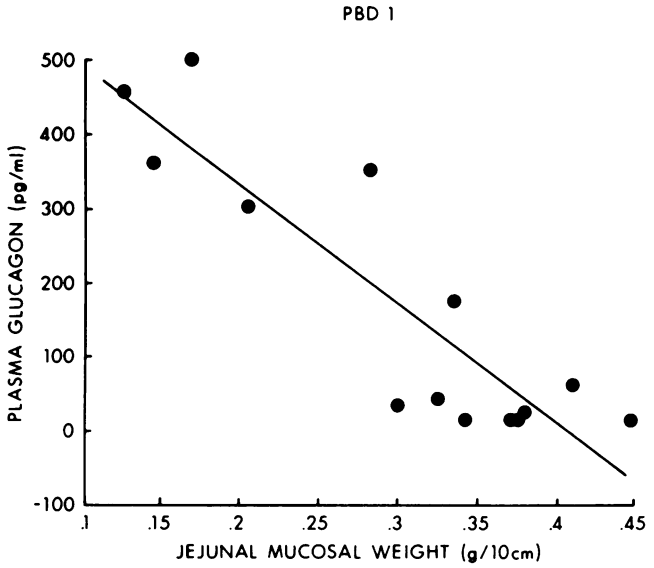


FIG. 6. Correlation between plasma glucagon level (pg/ml) and jejunal mucosal weight (g/10 cm) on PBD 1. $Y = -1598.2X + 650.30$, $N = 14$, $r = 0.888$, $p < 0.001$.

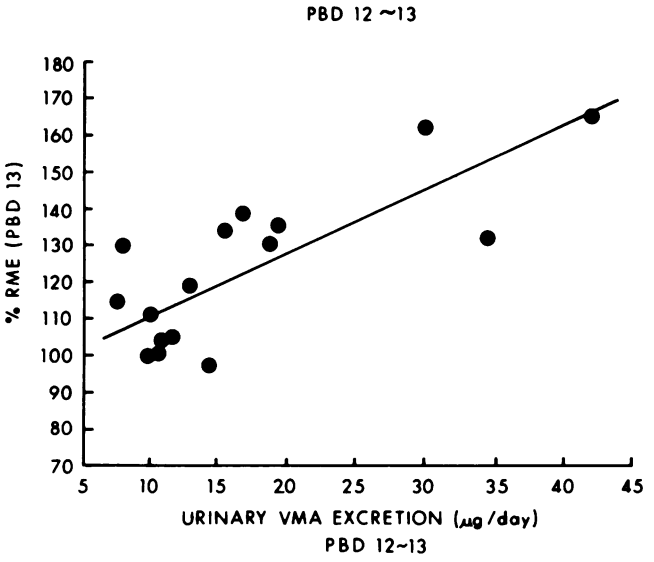


FIG. 8. Correlation between % RME (expressed as % of preburn level) and urinary VMA excretion (μg/day) on PBD 12–13. $Y = 1.66X + 94.77$, $N = 16$, $r = 0.739$, $p < 0.005$.

ureagenesis, decreases protein synthesis in liver,[40] and causes calorigenesis.[33] Orton et al.[41] reported a close correlation between plasma glucagon levels and the hypercatabolic state in burned patients. Considering the catabolic effects of cortisol and glucagon, the cause of severe weight loss seen immediately after burn in the groups with a 72-hour induction period might be due not only to the restriction of dietary intake, but also to the excessive secretion of those catabolic hormones. Indeed, from our preliminary studies (not reported), sham-burned guinea pigs (N = 7) similarly operated and fed intragastrically with the same 72-hour adaptation period as the 175 kcal-72 hour group, showed significantly heavier body weight than the burned comparative group just after the adaptation period (on PBD 3, 89.5 ± 0.9% *vs.* 84.8 ± 1.0% of original weight, $p < 0.02$). The EF group, which maintained these hormones at almost preburn level and received enough diet, maintained their body weight constantly.

Two weeks after burn, urinary VMA excretion, plasma cortisol, and plasma pancreatic glucagon levels were all lowest in the EF group (Table 6) and were all related to the RME for individual animals (Figs. 8–10). Considering the significant positive correlation between urinary VMA excretion and % RME, both of PBD 12–13 (Fig. 8) and

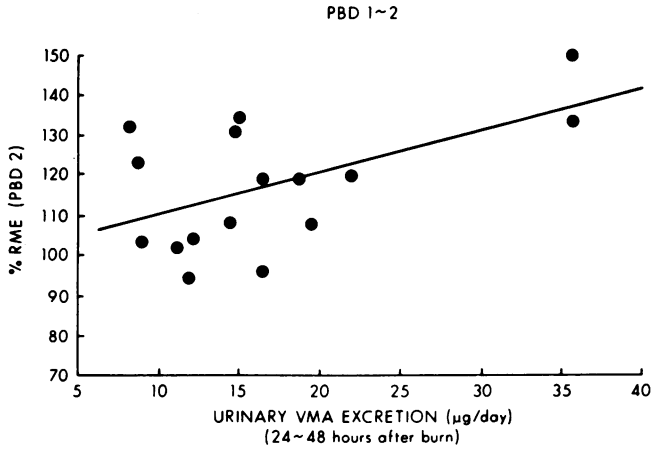


FIG. 7. Correlation between % RME (expressed as % of preburn level) and urinary VMA excretion (μg/day) on PBD 1–2. $Y = 1.06X + 99.52$, $N = 16$, $r = 0.548$, $p < 0.05$.

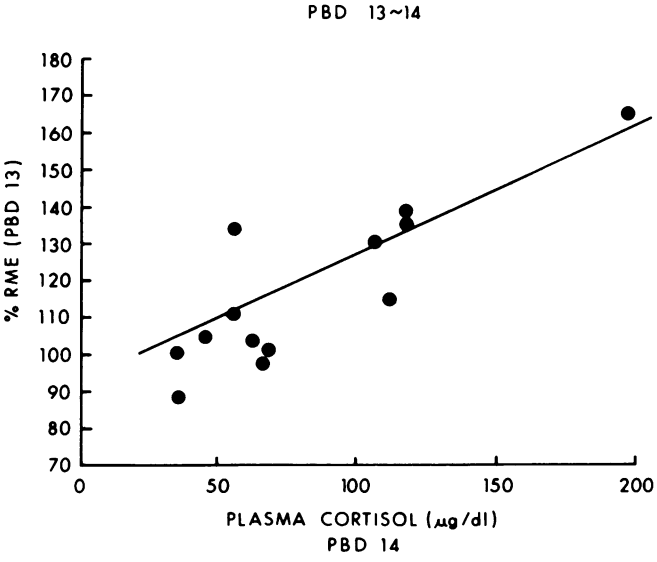


FIG. 9. Correlation between % RME and plasma cortisol (μg/dl) on PBD 13–14. $Y = 0.35X + 92.72$, $N = 14$, $r = 0.862$, $p < 0.001$.

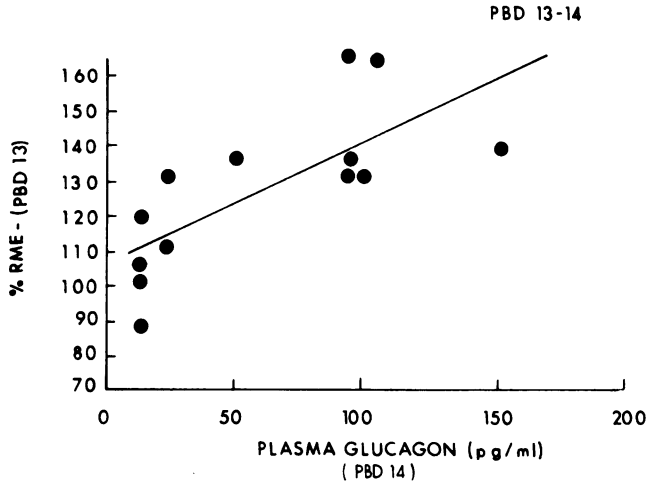


FIG. 10. Correlation between % RME and plasma glucagon (pg/ml) on PBD 13–14. $Y = 0.35X + 105.63$, $N = 13$, $r = 0.731$, $p < 0.01$.

PBD 1–2 (Fig. 7), catecholamines are undoubtedly a major mediator of the hypermetabolic response to burn injury throughout the postburn period, as indicated earlier.[2,13] However, since all animals with a 72-hour adaptation period showed higher RME on PBD 13 compared with that of PBD 2, and their individual urinary VMA excretion did not constantly increase with an increase in RME (Fig. 4), it is unlikely that catecholamines are the only hormones that are responsible for hypermetabolism after burn. There were also significant positive correlations between plasma cortisol and % RME (Fig. 9) and plasma glucagon and % RME (Fig. 10) 2 weeks after burn. These results are consistent with the findings of Alberti et al.[10] and Aulick et al.,[33] who pointed out those hormones had an influence on hypermetabolic response. However, since % RME and plasma cortisol or plasma glucagon showed different trends in the early postburn stage, it is unlikely that the effect of those two hormones on the metabolic rate might change according to the stage of postburn period. The prevention of excessive secretion of these catabolic hormones (catecholamines, cortisol, and glucagon) in EF group seemed to be a major reason for the reduction of hypermetabolic response to burn injury.

From our preliminary studies, jejunal mucosal weight of nonburned guinea pigs, bearing a catheter gastrostomy, given only 80 ml of LR solution for 24 hours ($N = 7$), was 293 ± 7 mg/10 cm, whereas burned guinea pig, similarly fasted (LR group, $N = 10$), had a jejunal mucosal weight of 221 ± 23 mg/10 cm ($p < 0.02$). Thus, burn injury itself has an influence on mucosal integrity. Our present finding shows that the decline of the intestinal mucosal integrity after burn can be prevented by immediate postburn intragastric feeding. It has been reported that the absence of oral or enteral feeding causes depletion of mucosal integrity even though complete nutritional support is provided intravenously.[19,42–44] Enteral feeding itself might, therefore, have an effect on preventing the postburn depletion of intestinal mucosal mass. Since there are highly significant negative correlations between the mucosal mass and plasma cortisol or plasma glucagon in the early postburn stage (Figs. 5, 6), it is suggested that enteral intake itself may have an influence on the regulation of hormonal secretion through the maintenance of intestinal mucosal integrity. It has been reported that plasma glucagon was elevated immediately after burn even though large amounts of glucose were administered intravenously.[37] High plasma cortisol has been reported in patients given traditional nutritional support with several days of semistarvation after burn,[10,45] but there has been no investigation concerning the effect of very early enteral feeding on the secretion of these hormones. To confirm the hypothesis that oral or enteral feeding beginning immediately after burn might be necessary for the prevention of excessive secretion of those hormones, a controlled study is needed using groups fed with identical formulations intravenously *versus* enterally.

The integrity of the intestinal mucosa might have a profound influence not only on its primary role, for example, digestion and absorption of diets, but also on its barrier function. Recent studies have shown that after a severe burn injury, translocation of indigenous gastrointestinal (G.I.) bacteria to other organs occurs as bacteria enter the circulation *via* the lymphatics from the gut.[46,47] Impairment of the G.I. mucosa was suggested by Deitch et al.[48] as a possible cause of postburn G.I. bacterial translocation.

Our working hypothesis to explain our findings fits nicely with the above observations. It is probable that both decreased blood flow and loss of enteral nutrition contribute to the rapid decline in mucosal cell mass of the small intestine following burn injury. With such a profound change, the barrier function to bacteria and endotoxin may be altered so that both enter the lymphatic circulation. Endotoxin would activate complement, known to occur in severe burn injury,[49,50] releasing a variety of split products that activate neutrophils and macrophages,[51,52] Activated macrophages, in turn, secrete large amounts of endogeneous pyrogen,[53,54] known to be identical to interleukin-1,[55] which enhances the catabolic response.[56] How these changes affect the secretion of catabolic hormones is unclear, but the associations as discussed above appear to be very real.

There were two patterns for elevation of RME after burn (Fig. 2). In the first type, seen in 175 kcal–72 hr group, RME increased rapidly to a high level by PBD 9 and reached to a plateau. In other types, seen in 200 kcal-72 hr group, RME remained at low level until PBD 6, then increased steeply and reached almost the same level as the former group at 2 weeks after burn. RME of the

175 kcal-72 hr group exceeded administered calories from the beginning of postburn period and was never satisfied (Tables 1 and 4). It is apparent that insufficient caloric administration might make the nutritional depletion worse in this group, and it is likely that this inadequate caloric supply and nutritional depletion could be a stress that might stimulate increased secretion of catabolic hormones and that those hormones drove the metabolic or catabolic response to very high levels. This explanation is consistent with the finding of Wolfe et al.[36] and our recent study[8] mentioned above, in which metabolic expenditure increased abruptly during the early postburn period in the burned guinea pigs fed with insufficient daily calories. On the other hand, although the 200 kcal-72 hr group received sufficient daily calories from PBD 3 to PBD 9 (Tables 1 and 4), RME increased after PBD 9. After the severe weight loss just after burn, the 200 kcal-72 hr group regained weight slightly until PBD 10 (Fig. 1). However, after that, the animals never reached the level that the EF group continuously maintained. Kien et al.[57] pointed out a significant correlation between RME and protein synthesis in recovering burn patients. According to their findings, once severe weight loss or nutritional decline occurs after burn, RME might increase to a higher level during the recovery period. This may be considered as one explanation of delayed onset of the increase in RME in the 200 kcal-72 hr group. When the provided calories cannot meet the increased need for resynthesis of lean body mass, secretion of the hormones such as catecholamines, cortisol, and glucagon might increase as a stress response.

The animals easily tolerated immediate postburn intragastric feeding and had neither diarrhea nor post-traumatic ileus. While previous reports contend that early feedings are not possible in patients because of ileus, other investigators have determined that post-traumatic ileus is caused mainly by the dysfunction of stomach and colon, not by the small bowel.[58–60] There are many reports that show intact motility and absorptive function of the small bowel in the very early period after operation,[61–64] and many papers point out the beneficial effect of enteral feeding immediately after major operations.[60,65,66] McArdle et al.[67] provided burn patients with an elemental diet starting 48 hours after burn by using a feeding tube placed transnasally into the duodenum, thereby avoiding infusion into the stomach. Patients fed in this manner were able to tolerate tube feeding at a rate of 125–150 ml/h (approximately 140 kcal/hr–170 kcal/hr) without developing any evidence of gastric dilatation or vomiting, with excellent nutritional maintenance, and high survival rate. Despite the 48-hr delay of initial nutritional support, they were still able to document better nutritional preservation than control patients who received traditional nutritional management.

Our findings in an animal model clearly show that initiation of intragastric feeding of a complete and sufficient diet immediately following a severe burn injury is associated with preservation of mucosal mass of the small intestine, inhibition of the expected response of catabolic hormones, inhibition of the expected rise in RME, and improved nutritional status. The concept of early enteral feeding to prevent hypermetabolism should be explored cautiously in man.

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